Remarks

Courtesies extended to Applicants' representative during the personal interview held on February 19, 2003 are acknowledged with appreciation.

In accordance with the present invention, there are provided chimeric proteins comprising a fusion of at least two functional protein units, wherein each functional protein unit comprises the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily (see Figure A schematic below showing 2 functional protein units, each containing a dimerization domain).

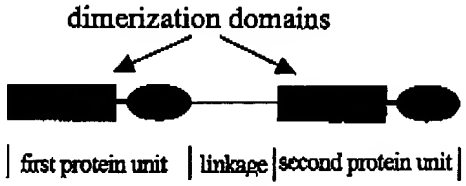


Figure A -- exemplary chimeric fusion protein construct

When these two protein units associate with each other (internal dimerization) or with another receptor member (dimerization with a dimer partner) the chimeric protein is capable of at least one function selected from the group consisting of DNA binding, ligand binding, transactivation and dimerization. Figure 7 from the specification is reproduced below. As discussed at the personal interview, a prior art native dimer is shown in Figure 7A, which illustrates how two dimerization domains from two independent polypeptides assemble. The present invention chimeric protein, which contains at least two dimerization domains within a single polypeptide, can adopt a variety of configurations, for example, disorganized (Figure 7B), as well as a variety of spontaneous dimer configurations; for example, an internal dimer or endodimer (Figure 7C), or various conformations with one or more dimer partners (Figures 7D-7F).

FIGURE 7A

Native Dimer

FIGURE 7B

Disorganized

FIGURE 7C

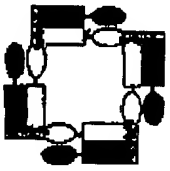
Endodimer

Trimer

FIGURE 7D

Tetramer

FIGURE 7E



Oligomer

FIGURE 7F

Claims 1-11 and 13-22 were pending before this communication. By this response, claims 1, 2, 4-6, 8-10 and 17 have been amended to define Applicants' invention with greater particularity. These amendments add no new matter and are fully supported by the specification and the original claims. Applicants respectfully submit that the amendments presented herein place the application in condition for allowance or, at a minimum, reduce the issues for appeal. Accordingly, entry of the amendments is respectfully requested.

Accordingly, claims 1-11 and 13-22 remain currently pending. The present status of all claims in the application, and current amendments thereto, are provided in the listing of claims presented herein beginning on page 2.

The rejection of claims 1-11, 13-22 and 52-54 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in the recitation of the term "functional entity", is respectfully traversed. Applicants' have previously amended claim 1 to recite four types of functions which

the chimeric proteins of the present invention are contemplated to possess. As discussed during the personal interview, these four functions are present upon formation of a functional entity, *i.e.*, association of the dimerization domains to form a spontaneous dimer. Moreover, the term "functional entity" or "functional dimer" is clearly defined in the specification (see, for example, specification, at page 11, line 26, through page 12, line 16). Therefore, Applicants respectfully submit that the subject term in claim 1 is clear when read in light of the specification.

However, in order to reduce the issues and expedite prosecution, claim 1 has been amended to specifically recite that the claimed "chimeric protein is capable of at least one function selected from the group consisting of DNA binding, ligand binding, transactivation and dimerization". Furthermore, as proposed at the personal interview, the term "functional entity" has been deleted at every instance (*i.e.*, claims 1, 2 and 4) in order to remove any possibility of confusion. In addition, claims 52-54 have previously been cancelled, and are therefore improperly included in this rejection. Accordingly, reconsideration and withdrawal of this rejection of claims 1-11, 13-22 and 52-54 under 35 U.S.C. § 112, second paragraph, are respectfully requested.

The rejection of claims 1-5, 14, 19 and 22 under 35 U.S.C. § 102(e), as allegedly being anticipated by U.S. Patent No. 5,830,462 to Crabtree *et al.* (hereinafter referred to as "the '462 patent"), is respectfully traversed. Applicants' invention clearly distinguishes over the '462 patent by requiring a chimeric protein comprising at least two functional protein units, wherein each unit comprises a dimerization domain. As such, only Applicants describe a single polypeptide capable of spontaneous dimerization either internally (endodimer) or with a dimer partner in various conformations as discussed above.

In further efforts to clarify that the chimeric protein is a single polypeptide, claim 1 has been further amended to recite that the at least two functional protein units of the chimeric protein are fused into a single polypeptide molecule by (i) fusion of said protein units, or (ii) use of a linker interposed between said protein units. In embodiment (i), the protein units may be

chemically coupled or recombinantly produced as a single polypeptide by fusing separate open reading frames of the nucleic acids encoding the protein units to form a single open reading frame as is known in the art (see specification, for example, at page 11, lines 19-22). In embodiment (ii), a linker is used between protein units, and can similarly be a chemical linkage of peptides or an amino acid linkage created recombinantly by adding nucleic acid sequence encoding the linker between the open reading frames encoding the protein units to form a single open reading frame as is known in the art (see specification, for example, at page 19, line 34, through page 21, line 20).

In contrast to the single polypeptide molecule contemplated by the present claims, the '462 patent teaches the association of two separate protein molecules. The '462 patent does not teach or suggest a chimeric protein comprising two dimerization domains, which can undergo internal dimerization, or optionally, dimerize with a dimer partner.

Furthermore, in contrast to the spontaneous dimerization achieved with the chimeric proteins of the present invention, the '462 patent teaches ligand-induced dimerization (see, for example, Figure 14 of the '462 patent). Indeed, the Examiner acknowledges that proteins of the '462 patent undergo "ligand-mediated oligomerization" (see Office Action, Paper No. 15, at page 4, lines 6-7). Thus, the '462 patent does not teach or suggest the use of any dimerization domains to achieve spontaneous dimerization.

Therefore, only the present application teaches a chimeric receptor where two functional protein units comprising two dimerization domains are present in a single polypeptide molecule capable of spontaneous association via the dimerization domains themselves. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 1-5, 14, 19 and 22 under 35 U.S.C. § 102(e).

The rejection of claims 1-11, 13, 14 and 19-22 under 35 U.S.C. § 103(a), as allegedly being unpatentable over the '462 patent in view of U.S. Patent No. 6,265,173 to Evans *et al* (hereinafter referred to as "the '173 patent"), is respectfully traversed. Applicants respectfully submit that neither reference, either taken alone or in combination, teaches a single polypeptide unit comprising at least two dimerization domains.

As noted above, the '462 patent does not teach or suggest a chimeric protein comprising at least two dimerization domains as claimed. The '173 patent is unable to cure the deficiencies of this primary reference, because it does not teach or suggest a single polypeptide unit comprising the combination of at least two dimerization domains. The '173 patent only contemplates multimeric species of a receptor member of the steroid/thyroid superfamily (containing a single dimerization domain) with an ultraspiracle receptor dimer partner (containing a single dimerization domain). Thus, the multimeric species disclosed in the '173 patent are the result of the dimerization of two independent molecules, each containing one dimerization domain.

Therefore, the chimeric protein of the present invention cannot be rendered obvious by the cited references. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 1-11, 13, 14 and 19-22 under 35 U.S.C. § 103(a).

Conclusion

In view of the above amendments and remarks, prompt and favorable action on all claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: April 21, 2003

Stephen E. Reiter
Registration No. 31,192
Telephone: (858) 847-6711
Facsimile: (858) 792-6773

FOLEY & LARDNER
Customer Number: 30542
30542
PATENT TRADEMARK OFFICE
P.O. Box 80278
San Diego, CA 92138-0278